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THE EPA REVIEW DRAFT:
HEALTH EFFECTS OF PASSIVE SMOKING: ASSESSMENT OF LUNG CANCER IN ADULTS AND RESPIRATORY DISORDERS IN CHILDREN

COMMENTS OF

PHILIP MORRIS INC.

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EXECUTIVE SUMMARY

We vigorously maintain that the Review Draft's classification of ETS as a Group A carcinogen is in error because it is not supported by the scientific evidence. The determination is based solely on an uncritical acceptance of several human epidemiological studies. Data from animal studies and short-term tests for genotoxicity in body fluids of nonsmokers do not support the epidemiologic estimates and are neither mentioned nor discussed in the Draft. Moreover, the exposure assessment in the Review Draft is inadequate; many studies showing that nonsmoker exposure to ETS is minimal are not referenced or discussed.

In addition, the Review Draft does not follow EPA's own guidelines for the evaluation of epidemiological studies (EPA 1986). For example, the notion of the strength of association is not applied to the epidemiologic studies on ETS. The cumulative increased risk estimate of 1.4 reported in the Review Draft is, by that very criterion, considered "weak" and explainable by confounding factors.

Individual weaknesses and published criticisms of the various epidemiological studies are not mentioned or assessed in the Draft. For example, the fact that no actual exposure data were collected in any of the epidemiologic studies was not addressed by the authors of the Draft.

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The notion of "statistical significance" for the individual epidemiologic studies was essentially ignored. Nineteen of the 24 studies mentioned in the Draft do not achieve statistical significance. This means that the data in those studies do not support rejection of the null hypothesis, i.e. there is no association between ETS and lung cancer in nonsmokers.

The Draft further ignores significant differences in the study designs, populations and protocols among the epidemiologic studies. Despite this, a meta-analysis is performed on the studies. The largest study on the issue was omitted from this analysis, while the most heavily criticized studies were included. The Draft did not address any of those published criticisms. Similarly, other published meta-analyses which do not agree with the Review Draft are not discussed.

The Review Draft addresses only one type of possible systematic bias in the epidemiologic studies; other sources of bias (e.g., exposure misclassification) and confounders (heredity, diet, use of cooking fuels, occupation, lifestyle), all of which are documented in the literature, are not mentioned.

The Draft does not address studies which assess workplace exposures (they report no significant increased risks), and it incorrectly characterizes epidemiologic studies conducted in the

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U.S. as representing a statistically significant increased risk for nonsmokers exposed to ETS.

The conclusion in Chapter Five of the Review Draft that ETS exposure affects the respiratory health of children is also scientifically unjustified. Many studies reporting no statistically significant increased risks between parental smoking and children's respiratory health are not addressed or discussed in the Draft; and equally important, many documented confounders are not considered.

Of particular interest is the inconsistency displayed by the Draft in the application of EPA's own guidelines for risk assessment. Recently, a draft risk assessment of electromagnetic fields (EMF) was released by the EPA. That risk assessment examined 40 epidemiological studies and all the available animal studies and short-term tests on the subject. It reported that the relative risks from the various studies averaged 3.0, and the authors concluded that those reported risks were not compelling enough to establish EMF as a Group B carcinogen. The ETS Review Draft, on the other hand, looked at only 24 studies which averaged half the increase in risks (1.41) noted in studies on EMF, and failed to consider pertinent animal and exposure data. The Draft nevertheless concluded that ETS is a Group A "(known human) carcinogen!"

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We do not believe that the Review Draft presents an objective or balanced analysis of the issue, and we urge rejection of its recommendation to classify ETS as a Group A carcinogen.

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EPA'S "WEIGHT OF THE EVIDENCE" CRITERIA

PROBLEMS IN ANALYSIS

COMMENTARY ON: The EPA's Review Draft "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children"

The Review Draft's recommendation to classify ETS as a Group A carcinogen is based upon a "weight of the evidence" argument which does not comply either with accepted scientific procedures or with the EPA's own guidelines for risk assessments.

The analysis presented in the Review Draft does not satisfy the EPA's own "weight of the evidence" procedure for determining human carcinogenicity. Those guidelines are as follows (EPA, 1986):

> The overall scheme for categorization of the weight of evidence of carcinogenicity of a chemical for humans uses a three-step process. (1) The weight of evidence in human studies or animal studies is summarized; (2) these lines of information are combined to yield a tentative assignment to a category and (3) all relevant supportive information is evaluated to see if the designation of the overall weight of evidence needs to be modified. Relevant factors to be included along with the tumor information from human and animal studies include structure-activity relationships; short-term test findings; results of appropriate physiological, biochemical, and toxicological observations; and comparative metabolism and

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pharmacokinetic studies. The nature of these findings may cause one to adjust the overall categorization of the weight of evidence. (Fed. Reg., 1986)

A. The Review Draft's analysis for the classification of ETS as a Group A carcinogen is based on the (uncritical) acceptance of human epidemiological studies alone.

B. The data from animal inhalation studies on ETS (sidestream smoke) are not considered: (Two published studies)

1. One sub-chronic (90-day) inhalation study (Adlkofer, 1988) reported no significant histopathological changes in the lungs of exposed animals;

2. A lifetime animal inhalation study using sidestream smoke reported no marked increase in tumor incidence among exposed animals (Haley, 1986, 1987, 1988).

3. None of the constituents in sidestream smoke identified as "potentially carcinogenic" has induced pulmonary cancer in animals under experimental conditions.

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C. Studies reporting results from short-term (in vitro) tests of ETS are not addressed in the Review Draft. A number of recent studies have reported no mutagenic activity in the body fluids of nonsmokers exposed to ETS. (Hoepfner, 1987; Scherer, 1987; Sorsa, 1989; Mohtashamipur, 1987; Martin, 1989, Scherer, 1990)

D. Exposure monitoring studies for ETS constituents published after 1985 were not considered in the Review Draft.

A number of recent studies employing state-of-the-art sampling equipment and procedures have concluded that nonsmoker exposure to ETS is minimal and, in some instances, orders of magnitude lower than levels predicted in the dose model developed in the Review Draft. (Appendix)

E. The Review Draft addresses only one form of potential bias in the human epidemiological studies on ETS. Other potential biases are not discussed and a number of substantiated confounding factors are ignored.

1. A commonly applied criterion for the adequacy of an epidemiologic association, namely, strength of association, is not mentioned in the Review Draft.

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Most of the individual studies on ETS and nonsmoker lung cancer incidence report odds ratios or relative risks of less than 1.5. Only five of the 23 published studies report statistically significant increased risks, which means that the data in 18 of the 23 studies do not permit rejection of the null hypothesis.

In a recently published review article, Dr. Ernst Wynder noted that "an association is generally considered weak if the odds ratio is under 3.0 and particularly when it is under 2.0, as is the case in the relationship of ETS and lung cancer" (Wynder and Kabat, 1990).

A positive association, with a statistically non-significant risk of less than 1.5, may be explained via confounding variables. Few of the existing studies on ETS and lung cancer considered such confounders.

The Review Draft does not comply with the EPA's own guidelines on the interpretation of epidemiologic studies. The guidelines state (EPA, 1986):

> Criteria for the adequacy of epidemiologic studies are well-recognized. They include factors such as the proper selection and characterization of exposed and control groups, the adequacy of duration and quality of follow-up, the proper identification and characterization of confounding factors and bias, the appropriate consideration of latency

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effects, the valid ascertainment of the causes of morbidity and death, and the ability to detect specific effects. Where it can be calculated, the statistical power to detect an appropriate outcome should be included in the assessment.

The EPA Guidelines continue:

Three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.

2. The possibility of confounding has been considered and ruled out as explaining the association.

3. The association is unlikely to be due to chance.

The Review Draft does not adequately address these criteria in its discussion of the epidemiological studies.

Studies not examined in the Draft have emphasized the importance of considering confounders in epidemiological studies on ETS. For example, in two papers published in 1988, Dr. Linda Koo re-analyzed her data on nonsmoking wives of smokers. Her results indicated that wives of nonsmoking husbands had "healthier" lifestyles than wives with smoking husbands; they exhibited higher socio-economic status and had better indices of family cohesiveness and lower frequencies of selected health problems and complaints. An important and statistically significant difference was found in the diets of the two groups. Wives with smoking husbands consumed

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more processed and spicy foods and ate fewer fresh fruits and vegetables than did wives of nonsmoking men. Koo concluded that such correlates of smoking status "act as important confounders when evaluating health risks among families with smoking husbands."

Four recently published reports, one from Japan and three from China, suggest that indoor pollution generated by kerosene heaters, coal stoves, liquefied petroleum gas and exposures to cooking oil vapors may be responsible for the increased risk of lung cancer among Oriental women. Moreover, in 1989, researchers in the U.S. reported that nonsmokers living with smokers consumed less carotene (Vitamin A) than did nonsmokers who lived with other nonsmokers. They concluded that "dietary beta-carotene intake is a potential confounder and should be measured whenever possible in studies of the relation between passive smoking and lung cancer."

Another kind of misclassification bias not addressed in the Review Draft may be a factor in the reported increase in lung cancer risks among nonsmokers, according to several scientists. For example, none of the studies on ETS and lung cancer provides direct observational information on ETS exposures. Instead, spouses, next-of-kin or friends are asked to estimate the amount of ETS to which they think the subject was exposed. Such estimates may lead to a kind of misclassification, called exposure misclassification, which has been shown by Garfinkel, Friedman and

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others to lead to improper indices of exposure and incorrect estimations of risk. In Garfinkel's 1985 study, for example, relative risks varied from 0.83 and 0.77 when the woman with lung cancer or the husband was the respondent, to a risk of 3.57 when a son or daughter responded. That means that the reported risk for lung cancer in the women exposed to ETS was less than the risk for women not exposed when either the women's or their husbands' estimates were used.

Dr. S. James Kilpatrick, a biostatistician from the Medical College of Virginia, has analyzed another form of misclassification, called differential misclassification, which results "from the tendency of respondents to inflate the amount of ETS exposure for lung cancer cases and deflate the report of exposure for controls." Similarly, Dr. Ernst Wynder, President of the American Health Foundation, notes that "relatives of nonsmoking lung cancer patients are more likely to report passive inhalation exposure on the part of their relative than are relatives of a control patient."

The Review Draft fails to address any of these kinds of confounders and potential biases.

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THE WEIGHT OF THE EVIDENCE

The Review Draft concludes that ETS is a Group A carcinogen based upon what is considered a "total weight of evidence" argument. The Draft provides six points in support of its conclusion (A-F):

A. Biological plausibility. ETS is taken up by the lungs and distributed throughout the body. The similarity of carcinogens identified in SS and MS along with the established causal relationship between lung cancer and smoking make it reasonable to suspect that ETS is also a lung carcinogen. (Review Draft)

Analysis:

1. The argument for dose in the Review Draft is based upon a model which does not employ data from recent exposure studies on ETS.

2. Not one epidemiological study on ETS and lung cancer collected actual exposure data; exposures were determined by answers to questionnaires.

3. The argument above contradicts the text in the Review Draft (4-15): "For example, MS and SS differ in the relative composition of carcinogens identified in tobacco smoke and in their physical and chemical

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properties in general. The lung and systemic distribution of chemical agents common to MS and SS are affected by the relative distribution between the vapor and particle phases, which differs between MS and SS and changes with SS as it ages." (emphases added)

4. No animal inhalation experiment using sidestream smoke has reported an increase in tumors among exposed animals.

5. None of the constituents in sidestream smoke identified as "potentially carcinogenic" has induced pulmonary cancer in animals under experimental inhalation conditions.

6. Short-term (in vitro) tests report no significant increases in mutagenic responses in body fluids of nonsmokers exposed to ETS.

7. The mainstream/sidestream smoke comparison does not pertain to ETS. ETS is a highly diluted, dynamic mixture which is qualitatively and quantitatively different from sidestream smoke, with constituent

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concentrations which are orders of magnitude smaller than those measured in sidestream smoke.

8. There is no known, acceptable mechanistic understanding of lung cancer in nonsmokers.

B. Consistency of response. The two completed cohort studies and sixteen of the 21 case-control studies observed a higher risk of lung cancer among the female never-smokers classified as exposed to ETS. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance. (Review Draft)

Analysis:

1. Of the 23 published studies on ETS and lung cancer in nonsmokers, only five report statistically significant increased risks. This means that the data in 18 of the 23 studies do not permit rejection of the null hypothesis, i.e., there is no association between ETS exposure and lung cancer in nonsmokers.

2. Perhaps as a result of the failure of individual studies to report consistently significant results, the Review Draft employs another method of statistical analysis which combines the reported results from numerous studies. With this method,

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called "meta-analysis," the authors claim to have calculated estimated excess risks for nonsmokers exposed to ETS that are 40 percent greater than those for non-exposed nonsmokers. In basic terms, they have reached these broad conclusions or "generalizations" by calculating an average of the relative risks for nonsmoker lung cancer cases reported by those studies. However, this method of generalization has been criticized for its questionable application to the epidemiological studies on ETS, due to the wide variety in their study designs, population selection, techniques of analysis and their results. This method also ignores basic methodologic weaknesses which, according to one recent governmental report, are characteristic of each published study on ETS and lung cancer. It further ignores the fact that the majority of studies considered in the various "meta-analyses" do not report statistically significant increases in lung cancer risks for nonsmokers. (Although the authors of several studies report risks which are not statistically significant, they report "positive" trends in their data. However, trends which fail the test for statistical significance do not support rejection of the null hypothesis, i.e., that there

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is no relationship between ETS exposures and lung cancer.)

3. In a recent analysis, Letzel and co-workers assessed the epidemiological studies on ETS for scientific rigor and then performed a meta-analysis on the pooled data from those studies (Letzel, 1988). There were 1023 possible combinations in the ten case-control studies examined by the researchers; only 24 of those combinations gave rise to statistically significant results. Moreover, the statistical significance in those 24 combinations was dominated by the presence of three studies of questionable scientific merit. The authors therefore concluded that any computed excess risk would be negligible and could not be used to support the claim that ETS exposures increase the risk of lung cancer in nonsmokers.

C. Upward trend in dose-response. Of the two major cohort studies, the Japanese study (Hirayama) demonstrates a strong association between passive smoking and lung cancer, including an upward trend in dose-response. The upward trend is well supported by the preponderance of evidence in the 13 case-control studies that classified data by exposure level. The Hirayama study has undergone extensive critical review that led to some corrections and revisions but failed to discredit the findings. Differences in life-style and culture may be a factor in the Japanese study reporting a stronger association

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between ETS and lung cancer than the American study (American Cancer Society). (Review Draft)

Analysis:

1. The Draft Risk Assessment correctly notes that the Hirayama study has been extensively criticized in the scientific literature. However, the EPA Draft is incorrect in its suggestion that the study has survived critical review. For example, in 1989, researchers reported that Hirayama had incorrectly adjusted the age of his study population (based on the husband's age) and that when correct age adjustments (based on the wife's age) are performed, the Hirayama study fails to achieve statistical significance (Ahlborn & Überla, 1988; Kilpatrick & Viren, 1988).

2. None of the 23 studies discussed above demonstrate a statistically significant dose-response relationship. The Japanese cohort study of Hirayama reported an inconsistent dose-response relationship when the subjects were stratified by the wife's age at the time of entry into the study (Hirayama, 1984).

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D. **Detectable association at environmental exposure levels. Within the population of women who are lifelong nonsmokers, the excess lung cancer risk of those married to a smoker is large enough to be observed. Carcinogenic responses are usually detectable only in high exposure circumstances, such as occupational settings or in highly dosed experimental animals. (Review Draft)**

Analysis:

1. No actual exposure data were gathered in any of the epidemiological studies on ETS and lung cancer. Exposure was assessed via questionnaire, with responses from spouses in some studies, from cases and relatives in others.

2. Confounders involved in being a "nonsmoking wife of a smoker" include occupation, diet and exposure to indoor/outdoor pollutants. The Review Draft did not address these confounders.

3. An estimated odds ratio of 1.4 is considered extremely "weak" by epidemiological standards and is, therefore, an inappropriate basis for an inference of causation.

4. The Review Draft's claim finds little or no support from actual animal inhalation experiments or short-

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term (in vitro) tests on either sidestream smoke or ETS.

E. Broad-based evidence. The 21 case-control and three prospective studies provide data from eight different countries and from a wide variety of study designs and protocols conducted by many different research teams. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies. (Review Draft)

Analysis:

1. Genetic factors, different diets, and different exposures to occupational and domestic substances may account for reported lung cancer rates among nonsmokers in different parts of the world. This is particularly true in Hong Kong and China, where lung cancer rates among nonsmoking women are excessively high. Research by Koo and others (1988, 1989) on diet and other exposures reports that spousal smoking does not account for this high incidence. Given the fact that most of the studies on ETS and lung cancer do not control for genetic factors, other exposures, diet, etc., the Review Draft's claim of "broad-based evidence" is dubious.

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2. The authors of the Review Draft are satisfied that they have effectively ruled out one potential bias, namely, the misclassification of smokers as nonsmokers. They did not address reporting bias.

3. Confounding factors, which were not addressed by the authors, need not be "broadly applicable across studies." By their own admission, the authors acknowledge the variable study designs, protocols and analysis used in the studies on ETS and lung cancer. Where one confounding factor such as the use of cooking fuels can explain the apparent positive associations reported in studies in China and Japan, other confounding factors, e.g., diet and occupation, may explain positive associations in studies conducted elsewhere.

F. Effects remain after adjustment for potential bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk from ETS exposure. The evidence remains statistically conclusive, however, after adjustments for smoker misclassification. The summary estimate of relative risk from raw data of both the case-control and cohort studies is 1.41 (95% C.I. 1.26, 1.57) before adjustment for misclassification and 1.28 (95% C.I. 1.12, 1.45) afterward (p. <0.01). (Review Draft)

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Analysis:

1. Other forms of misclassification are important and have not been addressed in the ETS-lung cancer studies. These kinds of misclassification include misclassification of disease and misclassification of exposure. For disease, few researchers have histologically confirmed the presence of actual primary lung cancers. In addition, all studies assessed exposure through questionnaires of various forms. Questionnaires are a notoriously inaccurate way to assess exposure. No actual exposure samples were taken in any study.

2. Such "adjustments" reported in the Review Draft for misclassification of smokers as nonsmokers are not consistent with those of Lee (1988, 1989) and Mantel (1987), who demonstrated that a misclassification bias of that sort would result in a statistically non-significant aggregate risk estimate for studies on ETS and lung cancer.

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Sidney, S., et al., "Daily Intake of Carotene in Nonsmokers with and Without Passive Smoking at Home," Am J Epi 129(6): 1305-1309, 1989.

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Sorsa, M., et al., "Cytogenetic Effects of Tobacco Smoke Exposure Among Involuntary Smokers," Mutation Research 222: 111-116, 1989.

Wynder, E.L., "Guidelines to the Epidemiology of Weak Associations," Prev Med 16: 211-212, 1987.

Wynder, E.L. and G.C. Kabat, "Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment," Indoor Air Quality, pp. 5-15, 1990.

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EXPOSURE ASSESSMENT: THE EPA REVIEW DRAFT

(1) No exposure data on ETS are included in the body of the EPA Report. Appendix C, Dosimetry of Environmental Tobacco Smoke, references a limited number of studies that predate 1985. However, other studies, many of which are more recent than 1985, report that nonsmoker exposure to ETS is minimal. These data contradict the dose model presented in the Review Draft.

The Review Draft omitted a substantial portion of scientific literature on ETS exposures. These papers include:

Baker, R.R., et al., "The Origins and Properties of Environmental Tobacco Smoke," Environment International 16: 231-245, 1990.

First, M., "Environmental Tobacco Smoke Measurements: Retrospect and Prospect," ETS-Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels, eds. R. Rylander, et al., Eur J Respir Dis, Suppl. 133(65): 9-16, 1984.

Jenkins, R. and M. Guerin, "Analytical Chemical Methods for the Detection of Environmental Tobacco Smoke Constituents," ETS-Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels, eds. R. Rylander, et al., Eur J Respir Dis, Suppl. 133(65): 33-46, 1984.

Bayer, C. and M. Black, "Thermal Desorption/Gas Chromatographic/Mass Spectrometric Analysis of Volatile Organic Compounds in the Offices of Smokers and Nonsmokers," Biomed Environ Mass Spect 14(8): 363-367, 1987.

Duncan, D. and P. Greavey, "Passive Smoking and Uptake of Carbon Monoxide in Flight Attendants," JAMA 251(20): 120-21, 1984.

Kirk, P., et al., "Environmental Tobacco Smoke in Indoor Air," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 99-112.

Yocom, J., "Indoor-Outdoor Air Quality Relationships," J Air Pollut Control Assoc 32(5): 500-520, 1982.

Cox, B. and M. Whichelow, "Carbon Monoxide Levels in the Breath of Smokers and Nonsmokers: Effect of Domestic Heating Systems," J Epidemiol Community Health 39: 75-78, 1985.

Girman, J. and G. Traynor, "Indoor Concentrations," J Air Pollut Control Assoc 33(2): 89, 1983.

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Gieseke, J., et al., "Collection and Characterization of Airborne Particulate Matter in Buildings," ASHRAE Transactions 84(1): 572-589, 1978.

Carson, J. and C. Erikson, "Results from Survey of Environmental Tobacco Smoke in Offices in Ottawa, Ontario," Environ Technol Letters 9: 501-508, 1988.

Sterling, T., "ETS Concentrations Under Different Conditions of Ventilation and Smoking Regulation," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 89-98.

Sterling, T. and B. Mueller, "Concentrations of Nicotine, RSP, CO and CO_2 in Nonsmoking Areas of Offices Ventilated by Air Recirculated from Smoking Designated Areas," Am Ind Hyg Assoc J 49(9): 423-426, 1988.

Proctor, C., et al., "Measurement of Environmental Tobacco Smoke in an Air-Conditioned Office Building," Present and Future of Indoor Air Quality, eds. C. Bieva et al. (Amsterdam: Excerpta Medica, 1989): 169-172.

Ogden, M. and K. Maiolo, "Collection and Analysis of Solanesol as a Tracer of Environmental Tobacco Smoke (ETS)," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 77-88.

Proctor, C., "The Analysis of the Contribution of ETS to Indoor Air," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 57-66.

Eatough, D., et al., "Assessing Exposure to Environmental Tobacco Smoke," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 131-140.

First, M., "Constituents of Sidestream and Mainstream Tobacco Smoke and Markers to Quantify Exposure to Them," Indoor Air and Human Health (Chelsea, Michigan: Lewis Publishers, 1985): 195-203.

Jenkins, R., et al., "Development and Application of a Thermal Desorption-Based Method for the Determination of Nicotine in Indoor Environments," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 557-566.

Muramatsu, M., et al., "Estimation of Personal Exposure to Ambient Nicotine in Daily Environment," Arch Occup Environ Health 59: 545-550, 1987.

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Thompson, C., et al., "A Thermal Desorption Method for the Determination of Nicotine in Indoor Environments," Environ Sci Technol 23: 429-435, 1989.

Foliart, D., et al., "Passive Absorption of Nicotine in Airline Flight Attendants," New Engl J Med 308(18): 1105, 1983.

Oldaker, G. and F. Conrad, "Estimation of Effect of Environmental Tobacco Smoke on Air Quality Within Passenger Cabins of Commercial Aircraft," Environ Sci Technol 21: 994-999, 1987.

Good, B., et al., "Effect of Cigarette Smoking on Residential NO_2 Levels," Environ Intl 8: 167-175, 1982.

Sega, K. and M. Fugas, "Nitrogen Dioxide Concentrations in Residences," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 493-496.

Hollowell, C. and R. Miksch, "Sources and Concentrations of Organic Compounds in Indoor Environments," Bull NY Acad Med 57(10): 962-977, 1981.

Biber, A., et al., "Determination of Nicotine and Cotinine in Human Serum and Urine: An Interlaboratory Study," Toxicology Letters 35(1): 45-52, 1987.

(2) The Review Draft does not adequately address the applications and limitations of exposure assessment data.

Indeed, in the EPA's "Strategies for Exposure Assessment Research," a report of the Exposure Assessment Subcommittee (1988), it is concluded that "there are still many unresolved exposure issues." This report notes that "the distribution of population ETS exposures is not known," and that the "relationship between ETS environmental concentrations and the deposited dose is important" (p. 12).

(3) The Dose Model in Appendix C is developed using respirable suspended particles (RSP) as a proxy for ETS. (See Preface of EPA draft, p. x-xi, and Section C.5.2, C-31). The average concentration of RSP is given as 200.0 $\mu g/m^3$ (Table C-3, C-22) and also according to Repace and Lowrey, 1980 (Table C-4, C-25).

This estimate is nearly twice as high as in a study of 44 offices, and from three to twenty times higher than the average RSP concentration reported in other studies of offices, buildings, restaurants and residents. These studies include:

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Weber, A. and T. Fischer, "Passive Smoking at Work," Int Arch Occup Environ Health 47: 209-221, 1980.

Sterling, T., et al., "Environmental Tobacco Smoke and Indoor Air Quality in Modern Office Work Environments," J Occup Med 29(1): 57-62, 1987.

Kirk, P., et al., "Environmental Tobacco Smoke in Indoor Air," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 99-112.

Gieseke, J., et al., "Collection and Characterization of Airborne Particulate Matter in Buildings," ASHRAE Transactions 84(1): 572-589, 1978.

Spengler, J., et al., "Long-Term Measurements of Respirable Sulfates and Particles Inside and Outside Homes," Atmos Environ 15: 23-30, 1981.

Carson, J. and C. Erikson, "Results from Survey of Environmental Tobacco Smoke in Offices in Ottawa, Ontario," Environ Technol Letters 9: 501-508, 1988.

Sterling, T., "ETS Concentrations Under Different Conditions of Ventilation and Smoking Regulation," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 89-98.

Sterling, T. and B. Mueller, "Concentrations of Nicotine, RSP, CO and CO_2 in Nonsmoking Areas of Offices Ventilated by Air Recirculated from Smoking Designated Areas," Am Ind Hyg Assoc J 49(9): 423-426, 1988.

Proctor, C., et al., "Measurement of Environmental Tobacco Smoke in an Air-Conditioned Office Building," Present and Future of Indoor Air Quality, eds. C. Bieva et al. (Amsterdam: Excerpta Medica, 1989): 169-172.

(4) The concentrations of cigarette smoke constituents (Table C-3) were calculated for fresh diluted sidestream smoke and serve as the basis (first step) of the mathematical model (C-21). However, ETS is not sidestream smoke; it is a dynamic and highly diluted mixture with constituent concentrations which are orders of magnitude lower than those recorded for fresh sidestream smoke.

References:

Baker, R.R., et al., "The Origins and Properties of Environmental Tobacco Smoke," Environmental International 16: 231-245, 1990.

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Eatough, D.J., et al., "The Chemical Characterization of Environmental Tobacco Smoke," Proceedings of the International Symposium at McGill University, eds. D. J. Ecobichon and J. M. Wu (Lexington: Lexington Books, 1990): 3-39.

Nystrom, C. and C. Green, "Assessing the Impact of Environmental Tobacco Smoke on Indoor Air Quality: Current Status," Presentation, ASHRAE Indoor Air Quality Conference, Atlanta, GA, April 21, 1986.

(5) Pertinent studies using ambient nicotine as a marker for ETS are neither referenced nor discussed in the Review Draft.

For example, Muramatsu (1987) measured the exposure level of ambient nicotine with a personal monitor carried by a nonsmoker and estimated the nicotine inhaled to be "equivalent to the amount of nicotine inhaled through active smoking from 0.003 to 0.010 ordinary cigarettes/h" (p. 546). In Thompson, et al. (1989), the Tenax method was used to determine nicotine concentrations in a number of restaurants. Other investigators measured nicotine in commercial flights with the same briefcase contained sampling system; the mean nicotine concentration of nonsmoking and smoking sections correspond to estimated mean exposures of 0.0041 and 0.0082 cigarette equivalent per flight, respectively.

References:

Jenkins, R., et al., "Development and Application of a Thermal Desorption-Based Method for the Determination of Nicotine in Indoor Environments," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 557-566.

Muramatsu, M., et al., "Estimation of Personal Exposure to Ambient Nicotine in Daily Environment," Arch Occup Environ Health 59: 545-550, 1987.

Thompson, C., et al., "A Thermal Desorption Method for the Determination of Nicotine in Indoor Method for the Determination of Nicotine in Indoor Environments," Environ Sci Technol 23: 429-435, 1989.

(6) The calculation in Appendix C for the nicotine/cotinine dose is based on the assumption that "cotinine is widely considered to be the preferred biomarker for ETS exposure" (See C-26). However, many scientists have recently observed that cotinine is not a good quantitative marker for ETS exposures, due to inter-individual and intra-individual variations in metabolism and clearance.

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References:

Johnson, L., et al., "Passive Smoking Under Controlled Conditions," Int Arch Occup Environ Health 56, 1985: pp. 99-110.

Letzel, H., et al., "Measuring Problems in Estimating the Exposure to Passive Smoking Using the Excretion of Cotinine," Toxicology Letters 35(1): 35-44, 1987.

Biber, A., et al., "Determination of Nicotine and Cotinine in Human Serum and Urine: An Interlaboratory Study," Toxicology Letters 35(1): 45-52, 1987.

Schwartz, S., et al., "Mathematical Modelling of Nicotine and Cotinine as Biological Markers of Environmental Tobacco Smoke Exposure," Toxicology Letters 35(1): 53-58, 1987.

Balter, N., et al., "Application of Physiological Pharmacokinetic Modeling to the Design of Human Exposure Studies with Environmental Tobacco Smoke," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 179-188.

A more recent study, by Haley, et al. (1989) reports that "differences in the mode of uptake and absorption of nicotine and possible differences in nicotine metabolism may play roles in the clearance rate differences [found] between smokers and nonsmokers" (p. 1048).

Another recent study (Curvall, et al., 1990) concludes that "metabolism of nicotine to cotinine and the elimination of cotinine are not dose-dependent at the low dose of nicotine to which nonsmokers are exposed by environmental tobacco smoke" (p. 48).

Coultas, et al. (1989) report: "In adults, the weak relation between cotinine level and reported smoke exposure implies that a single cotinine measurement should not be used to estimate exposure for individuals" (p. 346).

Henderson, et al. (1990) also find that cotinine assays "appear less accurate in distinguishing persons who are routinely exposed passively to ETS from those who are sporadically exposed. Furthermore, our knowledge of the usefulness of cotinine determinations for ranking the intensity of passive smoke exposure in populations of individuals is fragmentary" (p. 199).

A recent interlaboratory study (Watts, et al., 1990) stated: "Cotinine levels reported for nonsmokers were extremely variable, and a number of laboratories could not detect cotinine

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in serum from exposed nonsmokers. In addition, cotinine values reported by some laboratories have no relationship to estimated ETS exposure, or they were so high as to be unrealistic" (p. 179).

References:

Haley, N.J., et al., "Elimination of Cotinine from Body Fluids: Disposition in Smokers and Nonsmokers," Am J Public Health 79(8): 1046-1048, 1989.

Curvall, M., et al., "Simulation and Evaluation of Nicotine Intake During Passive Smoking: Cotinine Measurements in Body Fluids of Nonsmokers Given Intravenous Infusions of Nicotine," Clin Pharmacol Ther 4(1): 42-49, January, 1990.

Coultas, D.B., et al., "Questionnaire Assessment of Lifetime and Recent Exposure to Environmental Tobacco Smoke," Am J Epidemiol 132(2): 338-347, 1989.

Henderson, F.W., et al., "Home Air Nicotine Levels and Urinary Cotinine Excretion in Preschool Children," Am Rev Respir Dis 147: 197-201, 1990.

Watts, R.R., et al., "Cotinine Analytical Workshop Report: Consideration of Analytical Methods for Determining cotinine in Human Body Fluids as a Measure of Passive Exposure to Tobacco Smoke," Environmental Health Prospectives 84: 173-182, 1990.

(7) The dose calculations presented in Appendix C are selective and misleading.

Examples:

Selective -- The measurements of ETS constituents in environmental settings (Table C-4) are adapted entirely from the Repace (1987) review.

Misleading -- The ratio of measures (ETS/MS) calculated in Appendix C (Table C-7) is designated as "very large" in seven instances relating to the vapor phase of nicotine and cotinine. This is not a reasonable quantitative measure.

Thus, the dose model in Appendix C does not fulfill the requirements (EPA, 1986) for establishing an exposure assessment. Much of the published literature on ETS exposure is ignored, and uncritical acceptance of certain input values (e.g., cotinine) renders the model unusable for determining dose.

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ANIMAL STUDIES

No consideration is given to animal studies or short-term tests in the EPA Review Draft's "weight of the evidence" argument. The results of these studies provide no support for the claim that ETS is a carcinogen.

The results of the only two published studies involving sidestream smoke inhalation in animals are summarized below.

Adlkofer, et al., 1988:

F-344 rats and Syrian golden hamsters were exposed to sidestream smoke (SS) of Kentucky reference cigarettes for 90 days. (Concentrations of SS were 100 times higher than the smoking-related particulate levels reported for real-life situations.)

-- Histopathological examination of the respiratory tract revealed no significant differences between SS-exposed animals and controls.

-- No lung tumors developed.

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Haley, et al., 1988:

Syrian golden hamsters were whole-body exposed to sidestream smoke for 18 months.

-- No significant increase in tumor incidence in treated animals was observed.

In his comprehensive review of the literature on suspected pulmonary carcinogens, Aviado (1988) observed that none of the constituents in sidestream smoke which have been identified as "potentially carcinogenic" have induced pulmonary cancer in animals under experimental conditions.

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REFERENCES

Adlkofer, F., et al., "Exposure of Hamsters and Rats to Sidestream Smoke of Cigarettes: Preliminary Results of a 90 Day Inhalation Study," In: Perry, R. and Kirk, P. (eds.), Indoor and Ambient Air Quality, (London: Selper Ltd., 1988): 252-258.

Haley, N. and Hoffman, D., Progress report of an on-going study (1981-1992) entitled "Experimental Tobacco Carcinogenesis" submitted to the Department of Health and Human Services, Public Health Service, 1988.

Aviado, D., "Suspected Pulmonary Carcinogens in Environmental Tobacco Smoke," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper Ltd., 1988): 141-146.

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SHORT-TERM TESTS

The Review Draft, in its "weight of the evidence" approach, fails to consider published results on short-term tests. Several recent studies have reported no mutagenic activity attributable to ETS (environmental tobacco smoke) exposure in the body fluids of nonsmokers. A summary of those results follows:

Hoepfner, et al., 1987:

-- Increases in hydroxyphenanthrene result in positive mutagenicity test results.

-- Although a diet rich in polycyclic aromatic hydrocarbons (PAHs) leads to a significant increase in urinary hydroxyphenanthrene, levels of hydroxyphenanthrene in nonsmokers exposed to ETS were not significantly increased.

Scherer, et al., 1990:

(Biomonitoring included determination of COHb, cotinine, urinary excretion of 5 different monohydroxyphenanthrenes, thioethers, and a determination of their mutagenic activity.)

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-- Common biomarkers only indicate exposure to gas phase constituents of ETS.

-- Exposure to ETS particles appears to be undetectable.

-- No mutagenic activity was reported for ETS-exposed individuals.

Martin, et al., 1989:

-- A diet containing elevated levels of PAH caused a slight increase in monohydroxyphenanthrene (OH-PHE) excretion.

-- A considerable increase in OH-PHE excretion was found in occupationally exposed subjects (road pavers and wood creosote workers).

-- Even in conditions of extraordinarily "high" concentrations of ETS and unrealistically long exposure times, no difference in urinary OH-PHE was observed in exposed and nonexposed nonsmokers.

Page D-26 of the Review Draft states: "Other genetic damage tests such as chromosomal aberrations and sister chromatid exchanges (SCE), may also be useful in determining deliverable

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target dose information for smokers and nonsmokers exposed to ETS." The following results were obtained in 3 studies that addressed these specific issues.

Sorsa, et al., 1985:

-- Passive smoking did not significantly effect blood COHb, thiocyanate, urinary thioethers, or SCE frequency.

-- No significant difference in urinary mutagenicity between exposed nonsmokers and controls was noted.

Husgafvel-Pursiainen, 1987:

-- No significant increase was observed in the lymphocyte SCE level in the group of non-smokers with a long-term exposure to ETS.

Sorsa, et al., 1989:

-- No induction of chromosome aberrations or SCE's was reported for non-smoking restaurant personnel.

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REFERENCES

Hoepfner, I., et al., "Hydroxy-phenanthrenes in the Urine of Non-Smokers and Smokers," Toxicology Letters, 35: 67-71, 1987.

Husgafvel-Pursiainen, K., "Sister-Chromatid Exchange and Cell Proliferation in Cultured Lymphocytes of Passively and Actively Smoking Restaurant Personnel," Mutation Research, 190: 211-215, 1987.

Martin, F., et al., "Urinary Excretion of Hydroxyphenanthrenes After Intake of Polycyclic Aromatic Hydrocarbons," Environment International 15: 41-47, 1989.

Scherer, G., et al., "Importance of Gas Phase and Particulate Phase Constituents in Exposure to Environmental Tobacco Smoke (ETS)." In: Lunau, F. and Reynolds, G.L. (eds.), "Indoor Air Quality and Ventilation," (London: Selper Ltd. 1990): 195-202.

Sorsa, M., et al., "Passive and Active Exposure to Cigarette Smoke in a Smoking Environment," Journal of Toxicology and Environmental Health, 1(b): 523-534, 1985.

Sorsa, M., et al., "Cytogenetic Effects of Tobacco Smoke Exposure Among Involuntary Smokers," Mutation Research, 222: 111-116, 1989.

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APPROPRIATENESS OF META-ANALYSIS: EPIDEMIOLOGICAL STUDIES ON ETS AND LUNG CANCER

The statistical procedure of meta-analysis treats the results of individual studies as individual data points in an overall analysis. It has been used effectively in combining the results of randomized, controlled clinical trials of pharmaceuticals. Such studies are eminently comparable because their methodologies and study populations are very similar.

More recently, meta-analysis has been used to analyze the results of epidemiological studies, that is, to calculate an overall relative risk from a weighted average of the relative risks of many studies. Because of the inherent differences in study design, methodology, and sample population, especially in the case of epidemiological studies on ETS and lung cancer, questions have been raised regarding the appropriateness of using this procedure to analyze epidemiological data.

The United States Environmental Protection Agency (EPA) used a meta-analysis (the extended Mantel-Haenszel procedure) to calculate an estimated overall relative risk for lung cancer related to exposure to environmental tobacco smoke (ETS); the results of this procedure are presented in Chapter 4 of their recent Review Draft "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children."

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The following points are pertinent published comments on the use of meta-analysis for studies on ETS.

1. Letzel and Überla, 1990.

-- Conducted meta-analyses on all possible case-control study combinations of the ETS-lung cancer literature.

-- The Trichopoulos, et al. study (1981) was involved in 330 of 353 significant study combinations, showing that one individual study can dominate the outcome of this analytical procedure.

-- These authors concluded that the Trichopoulos, et al. study was methodologically flawed.

2. Lee, 1990.

-- The following limitations of epidemiology could have contributed to bias in the epidemiological evidence on ETS and lung cancer analyzed by meta-analysis:

- The study population may not be representative of the overall nonsmoking population.

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- In general, the studies have small sample sizes.
- Possible confounding factors have not been taken into account in all the studies.
- The choice of controls was inappropriate in some studies.
- Lung cancer diagnosis was inaccurate in some studies.
- The studies may not be representative of all those that have been carried out; in particular, the earliest studies (Hirayama and Trichopoulos, et al.) showed positive results but few subsequent studies reported statistically significant results.
- No actual measurements of ETS exposure were taken in any of the studies; reliance on questionnaires generates inaccurate exposure information.
- Smoking status of the subjects may not be accurately classified.

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3. Mantel, 1990.

-- Reviews the results of two meta-analyses, by Blot and Fraumeni and by Wald, et al.

-- Among other criticisms, he states that "there was uncritical acceptance of the results of all the studies" in the two meta-analyses.

-- Also, Mantel proposes that "it would not take much false reporting [of nonsmoking status] to account fully for the seeming association between passive smoking and lung cancer."

-- Finally, he concludes: "What with subtle biases, not so subtle biases, and even extravagant errors, one should not accept too readily claimed demonstrations of ill effects of passive smoking."

Given the inherent weaknesses of the individual studies on ETS and lung cancer, together with the diverse nature of the study populations, and differences in design, protocol and data analysis, meta-analysis is inappropriate for application to these studies.

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REFERENCES

1. Letzel, H. and K. Überla, "Meta-Analyses on Passive Smoking and Lung Cancer," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 316-322.

2. Lee, P., "Increased Risk of Lung Cancer in Non-smokers Married to Smokers: A Result of ETS Exposure or of Bias?" Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 25-36.

3. Mantel, N., "What is the Epidemiologic Evidence for a Passive Smoking-Lung Cancer Association?" Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 341-347.

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CRITICISMS OF THE HIRAYAMA (1981) STUDY

In Chapter 3 of the Review Draft "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children," the United States Environmental Protection Agency (EPA) reviews the two major cohort studies on environmental tobacco smoke (ETS) exposure and lung cancer incidence. One of these, Hirayama's 1981 study of Japanese women, has been extensively criticized in the scientific literature. The EPA claims that Hirayama has "adequately addressed" criticisms of his study, and that "previous challenges to Hirayama's work regarding data analysis and other issues appear to have been resolved, aside perhaps from the issue of misreported smoking habits" (p. 3-34).

While this statement acknowledges that Hirayama's work has been criticized, it does not convincingly address the magnitude of the criticisms appearing in the scientific literature (see, e.g., Aviado, 1988; Gostomzyk, 1982; Lee, 1982; Lehnert, 1981).

The following paragraphs list some of the points raised by Hirayama's critics, and include, if available, Hirayama's responses.

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-- The study was not designed to investigate ETS exposure and lung cancer incidence (Kilpatrick, 1989, 1990; Überla and Ahlborn, 1990). This study, at most, generates a hypothesis about the relationship, and cannot be used to prove or disprove the hypothesis.

-- The age distribution of the sample is not representative of the total Japanese population, particularly for women over the age of 40 (Überla and Ahlborn, 1990). When a statistical correction is made for this bias, the increased relative risk reported by Hirayama virtually disappears.

-- The appropriateness of Hirayama's standardization of the data by husband's age, rather than by subject's, has been questioned (MacDonald, 1981a; Lee, 1982; Kilpatrick and Viren, 1988; Kilpatrick, 1989). When Kilpatrick re-analyzed the data adjusted by subject's age, the model used by Hirayama was shown to be inappropriate and the reported significantly elevated risk associated with husband's smoking was no longer apparent.

-- Errors in the original risk ratios and confidence intervals were noted and were publicly acknowledged by Hirayama (Lee, 1981; Hirayama, 1981c). Close review of the data in Hirayama's 1981 and 1984 papers reveals additional anomalies

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(e.g., Rutsch, 1981) and internal inconsistencies suggestive of possible selection bias (Layard and Viren, 1989).

-- Some of Hirayama's statistical techniques have been questioned (Mantel, 1981, 1983). For a study of a rare event (lung cancer) in a large population, use of the "p" value alone to analyze statistical significance may not be appropriate (Diamond and Forrester, 1983).

-- Use of the death certificate as evidence for lung cancer is known to be unreliable (Überla and Ahlborn, 1990).

-- Autopsy or histology results were available for only 11.5% (23 of 200) of the cases (Überla and Ahlborn, 1990). In a sample of 23 cases, 17 were adenocarcinoma (Kabat and Wynder, 1984). The results were not broken down by cell type, although the various cell types are believed to differ in their etiology and in their frequency of occurrence between the sexes (Grundmann, et al., 1981). Thus, Hirayama's assertion that all cases of lung cancer are attributable to ETS exposure is not sound (MacDonald, 1981a).

-- Only the smoking of the subject's husband was used as a surrogate measure for the subject's exposure to ETS (Kilpatrick, 1989). This indicator is neither reliable nor specific (Lehnert, 1981; Überla and Ahlborn, 1990).

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-- The smoking status of subjects was recorded only at the beginning of the study; confounding changes in smoking status during the duration of the study are thus not known (Kilpatrick, 1989).

-- The following confounding factors are not considered: ETS exposure outside the home, air pollution, occupation, diet, access to medical care, family history, lifestyle, home environment, overall changes in cancer incidence in Japan, socioeconomic status, or use of kerosene or coal heating and cooking sources (Sterling, 1981; Überla and Ahlborn, 1990).

-- Contrary to other studies, Hirayama reported a greater increase in lung cancer incidence in rural areas as opposed to urban areas (Grundmann, et al., 1981).

-- The health centers from which the sample was drawn were not randomly chosen (MacDonald, 1981a). Hirayama states that the "medically adequate" centers were selected. A sample chosen this way is not truly representative of the Japanese population (Lehnert, 1981).

-- It is possible to explain Hirayama's conclusions without reference to ETS exposure (Adlkofer, 1987).

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None of the issues mentioned above have been satisfactorily resolved (e.g., Kornegay and Kastenbaum, 1981; MacDonald, 1981b). In addition, Hirayama has not made his original data available for review (Adlkofer, 1987; Ahlborn and Überla, 1988; Überla and Ahlborn, 1990). Because the Hirayama study has a relatively large sample size, it has a disproportionate influence on the overall estimates of relative risk calculated by meta-analyses of the ETS/lung cancer data. It is, therefore, necessary that the criticisms of Hirayama's study presented in the scientific literature be completely addressed. The EPA Review Draft fails to justify the inclusion of the Hirayama study in its analysis.

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CRITICISMS OF THE TRICHOPOULOS, ET AL. (1981) STUDY

One of the case-control studies examining environmental tobacco smoke (ETS) exposure and lung cancer incidence is the 1981 study of Greek women by Trichopoulos and colleagues. Although this study is known to have many shortcomings, it is nevertheless cited as providing evidence for a significant excess lung cancer risk associated with ETS exposure.

The United States Environmental Protection Agency (EPA) includes the Trichopoulos, et al. study among the epidemiological studies used in preparing its Review Draft "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children." The EPA does not address the known deficiencies of this study nor does it attempt to justify including the study in the risk assessment.

The following paragraphs present criticisms of the Trichopoulos, et al. study from the published literature.

-- The shortcomings of the study were publicly acknowledged by the authors in the original publication: "This study has obvious limitations and is offered principally to suggest that further investigation of this issue should be pressed."

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-- In their 1990 paper on meta-analysis, Letzel and Überla evaluate the quality of the ETS-lung cancer studies. Based on possible sources of bias and other problems with study design, they conclude that the Trichopoulos, et al. study is "methodologically unacceptable" and is "a textbook example of how a case-control study should not be performed."

-- This study may strongly influence the outcomes of meta-analyses of the ETS-lung cancer epidemiological studies (the procedure used by the EPA) if it is included (Letzel and Überla, 1990). When the Trichopoulos study was included in meta-analyses of all possible case-control study combinations, it appeared in 330 of the 353 significant study combinations.

-- Cases and controls were chosen from different hospitals. This is inappropriate and may introduce a systematic bias (Lee, 1982, 1990).

-- Patients with adenocarcinoma and with alveolar carcinoma were excluded (Lee, 1982). This amounts to a selection bias among lung cancer cases regarding specific cell types.

-- The results reported by Trichopoulos, et al. could have arisen from misclassification of the husband's smoking habit, that is, misclassification of exposure (Kilpatrick, 1987).

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-- Only 65% of the cases were histologically or cytologically confirmed (Lee, 1982).

-- Interviewer bias is possible. One doctor selected and interviewed the controls, with full knowledge of the goals of the study (Trichopoulos, et al., 1981).

-- The smoking status of the husband was the only measure of ETS exposure considered (Trichopoulos, et al., 1981).

-- No confounding factors, including diet, were addressed (Trichopoulos, et al., 1981).

-- The small sample size is a limitation (Lee, 1982). According to Überla (1987), the small sample size means that "The statistically 'significant' results of this study may well be artefacts from chance, bias or confounding."

It has been shown that the Trichopoulos, et al. study, judged to be methodologically flawed, can have an overwhelming impact on the results of meta-analyses of the epidemiological studies on ETS exposure and lung cancer incidence. The EPA uses the results of a meta-analysis as the basis for a workplace smoking policy guide. The EPA's risk assessment does not address in any detail the flaws of the Trichopoulos, et al. study, nor does it

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correct for or show awareness of the possibility of one study dominating the results of the meta-analysis. These criticisms should be accounted for before the EPA's risk assessment is finalized.

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COMMENTS ON THE VARELA DISSERTATION (1987)

In 1987, a physician, Luis R. Varela, submitted a Ph.D. dissertation to Yale University entitled "Assessment of the Association Between Passive Smoking and Lung Cancer." This dissertation is a large case-control study of environmental tobacco smoke (ETS) exposure and lung cancer incidence in New York. Although the dissertation remains unpublished (following Dr. Varela's death), this study represents possibly the most comprehensive epidemiological study to date of this issue.

The Varela study concluded that the data showed no relationship between spousal smoking and an increased risk of lung cancer among nonsmokers, or between ETS exposure in the workplace and an increased risk of lung cancer among nonsmokers.

The United States Environmental Protection Agency (EPA) reviews the Varela dissertation in their recent Review Draft, "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children." However, the EPA fails to include the Varela study in its meta-analysis of the epidemiological evidence concerning ETS and lung cancer. It is this meta-analysis on which the EPA's risk assessment is based.

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While the validity of applying meta-analysis to epidemiological studies is questionable due to differences in methodology among studies and in characteristics of the various populations examined, given the methodological strength and large sample size of the Varela study, it appears that if a meta-analysis is to be done, Varela's study should be included.

The data from this study should be included because:

-- This is one of the few studies actually designed to test the hypothesis that lung cancer risk in nonsmokers is associated with [1] spousal smoking, [2] smoking by other members of the household, [3] exposure to ETS in the workplace, or [4] exposure to ETS in social situations. Many other studies in this area are re-analyses of data collected for other purposes.

-- The confounding factors of religion, income, marital status, and number of cigarettes smoked per day by former smokers were considered.

-- The sample size of the study (439 case-control pairs) is extremely large in comparison with other similar studies.

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-- Histological confirmation of the diagnosis of lung cancer by an expert reviewer was a condition for inclusion of a case in the study.

-- Cases and controls were matched by county of residence.

-- Direct interviews with the cases accounted for 67% of the responses. If it was necessary to use a proxy for the case, a matched proxy was obtained for the control as well.

-- Three measures of spousal smoking were used: number of cigarettes smoked per day, number of years of exposure, and a figure derived from these two, representing the number of cigarettes to which a person was exposed in a lifetime.

-- For spousal smoking, 73 statistical tests were run; none was significant. Because of the sample size of this study, the statistical power associated with these tests of statistical significance is extremely high.

-- For workplace smoking, only person/years of exposure were used. Twenty-seven tests of statistical significance were performed; none was significant.

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-- For smoking in social situations, measured as "units" of exposure, individual odds ratios were not significantly different from 1.0; however, a highly significant inverse trend between ETS exposure and lung cancer risk was noted.

-- Household exposure to ETS was measured as person/years of exposure. One exposure level, that for 175 or more person/years, had a significant odds ratio of 1.09. This represents living for 35 years in a household with 5 smokers. However, the significance becomes only marginal when confounding factors are considered (lower confidence limit of 1.0006).

The EPA's report states that Varela's results were not included in the Chapter 4 meta-analysis because the "raw data" were not made available. Given the statistical power associated with the size and strong methodological construction of this study, the EPA should include the data from this study in its analysis.

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REFERENCE

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OTHER EPIDEMIOLOGICAL STUDIES ON ETS AND LUNG CANCER

The Environmental Protection Agency calculates an overall relative risk based on epidemiological studies of exposure to environmental tobacco smoke and lung cancer incidence in the Review Draft "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children." However, the majority of the studies on this topic (19 of 24) have reported relative risks which are not statistically significant. In addition to the highly criticized studies of Hirayama (1981) and Trichopoulos, et al. (1981), the only statistically significant relative risks are the following:

-- Lam, et al., 1987. A relative risk for lung cancer of all cell types of 1.65 (95% confidence interval [CI] 1.16, 2.35) was reported, based on 115 women whose husbands smoked. When broken down by cell types, only the relative risk for adenocarcinoma was statistically significant.

-- Geng, et al., 1988. An overall odds ratio for nonsmoking women whose husbands smoked of 2.16 (95% CI 1.03, 4.53) was calculated, based on 34 cases.

-- Garfinkel, et al., 1985. Two analyses of the same data which produced apparently contradictory results were reported. A

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statistically significant dose-response relationship was reported between lung cancer incidence in female nonsmokers and the number of cigarettes smoked per day by their spouses. However, no significant relationship was observed between the occurrence of lung cancer in nonsmoking women and the total number of hours per day of exposure to ETS over either the past five or 25 years.

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EPIDEMIOLOGICAL STUDIES ON ETS AND LUNG CANCER: THE UNITED STATES

The epidemiological studies on environmental tobacco smoke (ETS) exposure and lung cancer incidence conducted in the United States provide no support for the EPA's claim that ETS is a known human carcinogen. Highlights of the conclusions of the nine United States studies follow.

1. Brownson, et al., 1987.

The odds ratio for adenocarcinoma in nonsmoking women exposed to 0-3 hours of ETS per day was 1.00. For the 10 women exposed to ETS for more than 4 hours per day, it was 1.68 (95% confidence interval [CI] 0.39, 2.97). The reported risk was not statistically significant.

2. Buffler, et al., 1984.

In a sample taken from several Texas counties, the odds ratios for lung cancer in nonsmoking men and women exposed to ETS were less than 1.0. For men, the odds ratio was 0.52 (95% CI 0.15, 1.74). For women, it was 0.78 (95% CI 0.34, 1.81).

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3. Correa, et al., 1983.

This study examined lung cancer incidence in Louisiana. For non-smoking men, a statistically non-significant overall odds ratio of 2.0 (no CI given) was calculated, based on only 2 cases. For women, the overall odds ratio, based on 14 cases, was 2.07; this, too, was not statistically significant. For 5 women exposed to 1-40 pack-years of their husband's cigarette smoke, the calculated odds ratio of 1.18 was not statistically significant. A statistically significant odds ratio of 3.52 was calculated for the 9 women exposed to 41 or more pack-years of their spouse's cigarette smoke. Because the sample sizes are extremely small, the calculated odds ratios should be viewed with caution.

4. Garfinkel, 1981.

In this very large cohort study, Garfinkel reported a mortality ratio for nonsmoking women of 1.27 (95% CI 0.85, 1.89) when husbands smoked less than 20 cigarettes per day. The mortality ratio was even lower, 1.10 (95% CI 0.77, 1.61), for women whose husbands smoked 20 or more cigarettes per day. The results were not statistically significant nor consistent with a dose-response relationship.

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5. Garfinkel, et al., 1985.

The authors present numerous odds ratios based on different classification schemes. Garfinkel, et al., provided two analyses of the same data which produced apparently contradictory results. While a statistically significant dose-response relationship was reported between nonsmoking female lung cancer patients and the number of cigarettes smoked per day by their spouses, no significant relationship was observed between the occurrence of lung cancer in nonsmoking women and the total number of hours per day of exposure to ETS over either the past five or 25 years.

6. Humble, et al., 1987.

In this study of Hispanic and non-Hispanic residents of New Mexico, an overall odds ratio of 2.9 was calculated for both males and females. The researchers used a 90% CI; it was 1.3, 6.7. For females only, the odds ratio was 1.8 (90% CI 0.6, 5.4). However, the sample size in this study was too small to allow the odds ratio to be corrected for both ethnicity and age at the same time. This lack of adjustment cautions against complete acceptance of these results.

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7. Kabat and Wynder, 1984.

No differences in ETS exposure were found between cases and controls, for both males and females. Odds ratios were not presented in the paper.

8. Varela, 1987.

In a very large study of New York State residents, Varela reported no statistically significant elevated risk for exposure from spousal smoking, exposure at the workplace or exposure in social settings. Of the numerous statistical tests that Varela conducted on spousal, workplace, or social exposure, none was statistically significant.

9. Wu, et al., 1985.

This study examined women with primary adenocarcinoma or small cell carcinoma in Los Angeles County, California. Adjusted risks for exposure to spouse's cigarette smoke were 1.2 (95% CI 0.6, 2.5) for adenocarcinoma patients, and 1.0 (95% CI 0.1, 7.6) for small cell patients. Neither odds ratio was statistically significant.

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9. Wu, A., et al., "Smoking and Other Risk Factors for Lung Cancer in Women," J Natl Cancer Inst 74(4): 747-751, 1985.

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EPIDEMIOLOGICAL STUDIES ON ETS AND LUNG CANCER: THE WORKPLACE

The risk assessment presented in Chapter 4 of the United States Environmental Protection Agency's (EPA's) Review Draft, "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children," is based on data from epidemiological studies which assessed ETS exposure in terms of spousal smoking rather than workplace exposure. Eight studies examined workplace exposure. None provided adequate support for risk associated with ETS exposure in the workplace:

-- Garfinkel, et al., 1985: No significantly increased risk of lung cancer in nonsmoking U.S. women was associated with exposure to ETS in the workplace. For exposure at work over the past five years, the odds ratio (OR) was 0.88 (95% confidence interval [CI] 0.66, 1.18). For workplace exposure over the past 25 years, the OR was 0.93 (95% CI 0.73, 1.18).

-- Kabat and Wynder, 1984: Preliminary data on exposure to ETS in the workplace were presented. Eighteen of 25 male cases reported ETS exposure at work, versus 11 of 25 controls. This difference was marginally significant (P = 0.05). For women, 26 of 53 cases reported exposure at work, as opposed to 31 of 53 controls, a non-significant difference.

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-- Koo, et al., 1987: ETS exposures in the home and in the workplace were examined for Hong Kong Chinese women. None of the adjusted odds ratios were significant at the 5% level.

-- Lee, et al., 1986: Several different indices of exposure, including the workplace, were considered. The authors conclude: "Overall the results showed no evidence of an effect of passive smoking on lung cancer incidence among lifelong nonsmokers. In male patients, relative risks were increased for some of the indices but number of cases were small and none of the differences approached statistical significance. In females, where number of cases were larger, such trends as existed tended to be negative..."

-- Shimizu, et al., 1988: The authors conclude: "Passive smoke exposure at work was not clearly associated with female lung cancer, although the relative risk was slightly elevated (RR = 1.2)." No confidence interval was provided.

-- Svensson, et al., 1989: For never-smoking Swedish women, the relative risk (RR) for ETS exposure, quantified as "At home or at work," was 1.2 (95% CI 0.4, 2.9). The relative risk for ETS exposure "At home and at work" was 2.1 (95% CI 0.6, 8.1). These results were not statistically significant.

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- Varela, 1987: Nine categories of exposure to ETS in the workplace were considered. These ranged from 1-25 person/years of exposure to greater than 175 person/years. None of the odds ratios was statistically significant.

-- Wu, et al., 1985: In a sample of nonsmoking white women in Los Angeles County, California, adjusted relative risks for ETS exposure at the workplace were 1.2 (95% CI 0.8, 2.2) for adenocarcinoma, and 2.3 (95% CI 0.7, 7.9) for small cell carcinoma. Neither of these was statistically significant.

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CHILDREN'S RESPIRATORY DISEASE

COMMENTARY:

"Environmental Tobacco Smoke and Respiratory Disorders in Children," Chapter 5, Review Draft: Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children

I. Overview: The Review Draft's discussion on "Environmental Tobacco Smoke and Respiratory Disorders in Children" does not provide a comprehensive review of the published literature and it does not provide sufficient analyses of important factors which pertain to the issue:

1. A substantial number of published studies conclude that there is no significant association between parental smoking and childhood respiratory symptoms, respiratory disease and lung function. These studies are neither cited nor discussed in the Review Draft. (A complete list of those studies and a synopsis of their respective conclusions appears in Section II below);

2. The authors of the Chapter do not address pertinent methodological issues common to published studies on parental smoking (see Section III below);

3. A number of important confounding variables are not addressed in the Draft. (For a complete summary of those confounders, see Section IV below);

4. Several recent published literature reviews on ETS and childhood respiratory disorders reach conclusions contrary to those of the Review Draft. Only one of those reviews is cited, and none are addressed by the authors of this Chapter. (See Section V below).

IIa. Synopses of published studies on ETS and childhood respiratory disorders reporting no significant associations and/or no effects from parental smoking:

1. Binder, R., et al., "Importance of the Indoor Environment in Air Pollution Exposure," Arch. Environ. Health 31(6): 277-279, 1976.

We found no evidence to support a cause and effect relationship between

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pollutant exposure and respiratory disease.

2. Camacho, E., et al., "Pulmonary Symptoms and Pulmonary Functional Tests Among Children in Relation to the Area of Residence," Eur Respir Dis 63(2): 165-166, 1982.

We have made an epidemiological study on a population sample of 1331 Catalan children who live in two different residential areas: 704 (322 girls and 382 boys) from an industrial area in the greater Barcelona area with considerable heavy traffic and industrial pollution, and 627 (311 girls and 316 boys) from four rural areas far from any focus of pollution.

Parental smoking habits and other family member smoking habits were analyzed. No difference in the number of cigarettes smoked daily in each area was observed nor any association with the presence of children's bronchial symptoms or with the history of airways disease.

3. Clifford, R.D., et al., "Prevalence of Respiratory Symptoms Among 7 and 11 Year Old Schoolchildren and Association with Asthma," Archives of Disease in Childhood 64: 1118-1125, 1989.

A new self administered questionnaire completed by parents was used to study the prevalences of wheeze, shortness of breath, and cough in 2503 Southampton schoolchildren aged 7 and 11 together with exacerbating factors and background information including treatment and diagnosis.

The overall prevalence of wheeze and shortness of breath in the current year (1986) were 12.1% and 8.5% respectively. Social class, home ownership, parental smoking, and presence of a family pet were unrelated to symptom prevalence.

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4. Gardner, G., et al., "Effects of Social and Family Factors on Viral Respiratory Infection and Illness in the First Year of Life," Journal of Epidemiology and Community Health 38: 42-48, 1984.

A total of 131 infants were monitored from birth through the first year of life for respiratory viral infection and illness and evaluated for the relationship that these had to certain social and familial factors.

No convincing differences for viral infection or respiratory illness were seen with parental smoking as an isolated factor.

5. Horwood, L.J., et al., "Social and Familial Factors in the Development of Early Childhood Asthma," Pediatrics 75(5): 859-868, 1985.

The role of social and familial factors in the development of childhood asthma by age 6 years was studied in a birth cohort of New Zealand children. Rates of asthma varied markedly with the child's sex; boys had twice the rate of asthma as girls.

Proportional hazards modeling of the data failed to show any significant associations between the development of asthma and a large range of other social and familial factors including breast-feeding, parental smoking habits, pets in the child's family, stress in the family, or social background.

6. Hosein, H.R., et al., "The Effect of Domestic Factors on Respiratory Symptoms and FEV_1," International Journal of Epidemiology 18(2): 390-396, 1987.

The largest effect on lung function was observed in children from homes with hot water heating systems, whereas the smallest effect was observed in children with smokers in

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the home. Children who lived in homes with hot water heating systems with no air conditioning had mean FEV_1 of up to 0.4 litres lower than did their counterparts who lived in homes with forced air heating and air conditioning.

Pets, heating systems, cooking fuel, crowding and passive smoking showed no consistent effects on the reporting of any of the symptoms. Girls who were exposed to the emissions from indoor hobbies reported more phlegm, wheeze and dyspnoea.

7. Kerrebijn, K.F., et al., "Chronic Nonspecific Respiratory Disease in Children, A Five Year Follow-up Study," ACTA Pediatrica Scandinavica Supplement 261, 1977.

Smoking and nonsmoking parents have about the same proportion of children with respiratory symptoms. The number of cigarettes smoked by the parents has no influence on respiratory symptoms in their children....

8. Lebowitz, M.D. and Quackenboss, J.J., "The Effects of Environmental Tobacco Smoke on Pulmonary Function," Indoor Air Quality, 1990.

A community study in Tucson is underway to evaluate the effects of environmental tobacco smoke (ETS) exposure on acute and chronic pulmonary function, including bronchial reactivity.

There were no significant relationships between ETS and allergic/irritant symptoms, for the entire sample by gender or for any age group, either independent of or controlling for PM10 in the house.

There was a slight increase of about 15% in the prevalence rate of daily acute respiratory illness symptoms

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in those homes with both ETS and PM10>50 ug/m^3 (Table 5)....

There was no relationship between the prevalence rates for chronic symptoms and diseases and the presence or amount of ETS in the home.

The lack of a relationship between ETS and chronic conditions is consistent with previous findings in Tucson (Lebowitz 1984).

9. Lebowitz, M., et al., "Respiratory Symptoms and Peak Flow Associated with Indoor and Outdoor Air Pollutants in the Southwest," JAPCA, 35: 1154-1158, 1985.

Utilizing indoor measurements showed that indoor levels of total and respirable particles were high in homes with smokers. However, there was no direct effect of ETS on children's symptoms or lung function. Indoor TSP had an effect on daily symptoms (eye irritation, productive cough) in all adults and on asthmatics' symptoms and PEF. However, since ETS did not, the relationships must be associated with other characteristics of the indoor TSP.

10. Ownby, D. and McCullough, J., "Passive Exposure to Cigarette Smoke Does Not Increase Allergic Sensitization in Children," J. Allergy Clin. Immunol., 82(4): 634-638, 1988.

The purpose of this study was to learn whether children passively exposed to parental cigarette smoke could be more frequently sensitized....

We conclude that children passively exposed to cigarette smoke do not produce more IgE to common allergens nor are they more likely to produce IgE to any particular allergen.

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11. Salzman, M., et al., "Passive Smoking and Croup," Arch. Otolaryngol. Head Neck Surg., 113: 866-868, 1987.

The relationship between croup and the presence of household cigarette consumption was assessed in a matched-pair case control study.

This study fails to show a relationship between passive smoking and croup in early childhood.

12. Sherman, C., et al., "Early Childhood Predictors of Asthma," American Journal of Epidemiology, 132(1): 83-95, 1990.

To investigate potential risk factors for the development of childhood asthma, the authors undertook a longitudinal study using a cohort of 770 children aged 5-9 years from East Boston, Massachusetts, that has been under study since 1975.

Neither bronchiolitis, eczema, croup, personal cigarette smoking, maternal smoking, paternal smoking, nor delivery complications bore an apparent relation to the development of asthma.

13. Watkins, C.J., et al., "Patterns of Respiratory Illness in the First Year of Life," British Medical Journal, 293: 794-796, 1986.

In this study the role of family health and social variables is not as clear cut as that reported by Leeder, et al. The striking finding in this study is the social class difference in frequency of consultations for respiratory illness, with high consultation rates for those whose fathers were in manual occupations. This is not explained by the fact that the families from which such children come are more likely to live in overcrowded conditions nor that the parents are

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more likely to smoke and have a productive cough....

IIb. Studies which report no significant associations between parental smoking and childhood respiratory disorders which were cited but not discussed in the draft analysis include:

1. Dodge, R., "The Effects of Indoor Pollution on Arizona Children," Archives of Environmental Health, 37(3): 151-155, 1982.

   No differences in pulmonary function or yearly lung growth rates occurred among subjects grouped by exposure to tobacco smoke or cooking fuel.

2. Koo, L., et al., "A Comparison of the Prevalence of Respiratory Illness Among Nonsmoking Mothers and Their Children in Japan and Hong Kong," Respiratory Illnesses Among Japanese and Chinese Mothers and Their Children, 290-295, 1988.

   A community survey of 314 nonsmoking mothers and their children in Hong Kong, and 243 mothers and children in Japan showed that the prevalence of reported chronic cough and sputum symptoms was 10 or more times higher in Hong Kong than in Japan.

   Occupational exposure to dust or fumes and larger household sizes were found to be associated with higher levels of respiratory illnesses among the Hong Kong mothers.

   For both populations, however, there was a highly significant correlation between the frequency of respiratory illnesses of each mother and her child.

3. Lebowitz, M., et al., "The Effect of Passive Smoking on Pulmonary Function in Children," Environment International, 8: 371-373, 1982.

   A study of ventilatory function was conducted in 344 nuclear families in a representative community population sample in Tucson, AZ. Household

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aggregation of pulmonary function, which is dependent on household aggregation of body mass, might affect the relationship of children's pulmonary function to parental smoking. When household aggregation of body mass was taken into account, there was no relationship of children's pulmonary function values to parental smoking.

4. Lebowitz, M., et al., "Family Aggregation of Pulmonary Function Measurements," Am. Rev. Respir. Dis., 129: 8-11, 1984.

Family aggregation of pulmonary function measurements was analyzed in the nuclear families of the Tucson epidemiologic study of airway obstructive diseases (AOD). There were 271 parental pairs and their natural children who had satisfactory pulmonary function data.

After controlling for the familial aggregation of body habitus, a major determinant of pulmonary function, there was no remaining independent aggregation of pulmonary function measurements. It was also determined that parental passive smoking had no effect on children's pulmonary function measurements.

5. Schilling, R.S.F., et al., "Lung Function, Respiratory Disease, and Smoking in Families," American Journal of Epidemiology, 106(4): 274-283, 1977.

Parental smoking had no effect on children's symptoms and lung function.

6. Speizer, F., et al., "Respiratory Disease Rates and Pulmonary Function in Children Associated with NO_2 Exposure," American Review of Respiratory Disease, 121(1): 3-10, 1980.

Children from households with gas stoves had a greater history of respiratory illness before age 2

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(average difference, 32.5/1,000 children) and small but significantly lower levels of FEV and FVC corrected for height (average difference, 16 ml and 18 ml respectively). These findings were not explained by differences in social class or by parental smoking habits.

IIc. Published criticisms of studies cited in the Draft Report received no discussion. For example, the paper by Strachan, et al., (1989) claimed that ETS is associated with an increased risk of middle ear effusion in children. Yet a published critique challenges that conclusion (C.J. Woodland, R.M. Terry, "Passive Smoking and Middle Ear Effusion in Children" BMJ, 299: 258-259, 1989). The authors note:

> Dr. Strachan and colleagues unfortunately do not seem to have checked their findings with otoscopy.
>
> A possible indicator of this fault can be found in their numbers of abnormal tympanograms with increasing cotinine concentrations. There seems to be a trend relating increasing incidence of flat tympanograms to cotinine concentration, but there is no such trend with negative middle ear pressure. If one assumes that the same pathological process causes both negative middle ear pressure and middle ear effusion through dysfunction of the eustachian tube then the association between passive smoking and middle ear effusion is quite likely to be spurious.

III. Issues of Methodology:

The Executive Summary suggests that "[t]he overall evidence of a health risk [from parental smoking] is based on numerous investigations that vary broadly in design and location, source of data, objective, protocol and methods of analysis" (1-9).

However, recent reviewers of the literature (Rubin and Damus, 1988; Witorsch and Witorsch, 1989) conclude that because the available studies differ widely in design, data acquisition,

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protocol, and methods of analysis, sweeping conclusions about increased health risks cannot be made.

For example, each of the studies has employed a different index of ETS exposure. Questions regarding ETS exposure frequency and duration differ from study to study. The Draft Report suggests that "there is no evidence to suggest that this method has been inadequate ..." (5-5). On the contrary, the published literature on ETS contains numerous studies regarding the differential accuracy in determining ETS exposure histories through questionnaire responses.[1-5]

Specific studies cited in the Review Draft have conceded that the reliance on questionnaires for information about respiratory symptoms casts doubt on the findings. In one study which reported a significant association between parental smoking and respiratory symptoms, for example, it was noted that even "slight changes" in the way the questions were phrased could result "in substantial differences in the type of responses one obtains" (Ekwo, 1983). Similarly, another study observed that there was a significant difference in the respiratory symptoms reported depending on which parent completed the questionnaire (Schenker, 1983).

None of the studies assessing ETS and childhood respiratory disorders verified exposure through actual ETS measurements in the air. All have relied upon questionnaires. The Draft Report notes that studies on cotinine concentrations in the body fluids of children may provide evidence concerning exposure to ETS among children (5-3). However, it is questionable whether or not a cotinine assay from one study may be legitimately correlated with health effects in another. Moreover, it has been recognized by many researchers that cotinine assays have a limited use in distinguishing between exposed and unexposed children and that cotinine cannot be used as a quantitative marker for ETS exposures. This is because there are great inter-individual and intra-individual differences in the metabolism and clearance of cotinine. (6-14) In addition, different methods of analysis may influence final recorded levels of cotinine.

In light of the pharmacologic and analytic properties of cotinine, it is misleading to suggest that it can be used to determine total exposures to ETS, and thereby provide a basis for a correlation with reported health effects.

1. Friedman, G., et al., "Prevalence and Correlates of Passive Smoking," American Journal of Public Health, 73(4): 401-405, 1983.

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2. Kilpatrick, S.J., Jr., "Misclassification of Environmental Tobacco Smoke Exposure: Its Potential Influence on Studies of Environmental Tobacco Smoke and Lung Cancer," Toxicology Letters, 35: 163-168, 1987.

3. Pron, G., et al., "The Reliability of Passive Smoking Histories Reported in a Case-Control Study of Lung Cancer," American Journal of Epidemiology, 127(2): 267-273, 1988.

4. Sandler, D. and Shore, D., "Quality of Data on Parents' Smoking and Drinking Provided by Adult Offspring," American Journal of Epidemiology, 124(5): 768-778, 1986.

5. Wynder, E., "Guidelines to the Epidemiology of Weak Associations," Preventive Medicine, 16: 211-212, 1987.

6. Adlkofer, F., et al., "Correspondence," The New England Journal of Medicine, 32(11): 719-721, 1985.

7. Balter, N.J., et al., "Application of Physiological Pharmacokinetics Modeling to the Design of Human Exposure Studies with Environmental Tobacco Smoke"

8. Bibi, A., et al., "Determination of Nicotine and Cotinine in Human Serum and Urine: An Interlaboratory Study," Toxicology Letters, 35: 45-52, 1987.

9. Haley, N., et al., "Elimination of Cotinine From Body Fluids: Disposition in Smokers and Nonsmokers," American Journal of Public Health, 79(8): 1046-1048, 1989.

10. Johnson, L.C., et al., "Passive Smoking Under Controlled Conditions," Int. Arch. Occup. Environ. Health, 56: 99-110, 1985.

11. Letzel, H., et al., "Measuring Problems in Estimating the Exposure to Passive Smoking Using the Excretion of Cotinine," Toxicology Letters, 35: 35-44, 1987.

12. Orssaud, G., et al., "Intéret De La Determination De Differents Marqueurs Biotoxicologiques De L'exposition Tabigique Passive," Sem. Hop. Paris, 65: 2467-2468, 1989.

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13. Schwartz, S., et al., "Mathematical Modelling of Nicotine and Cotinine as Biological Markers of Environmental Tobacco Smoke Exposure," Toxicology Letters, 35: 53-58, 1987.

14. Watts, R., et al., "Cotinine Analytical Workshop Report: Consideration of Analytical Methods for Determining Cotinine in Human Body Fluids as a Measure of Passive Exposure to Tobacco Smoke," Environmental Health Perspectives, 84: 173-182, 1990.

IV. Confounding Factors

While the Executive Summary states that "most studies [on parental smoking] have controlled for bias and potential confounding factors to the extent possible," a closer look at relevant literature reveals that this is not the case (see e.g. NIH, 1983; Rubin and Damus, 1988; R. Witorsch, 1990). Indeed, of the many confounders reported in the literature, Chapter 5 of the Review Draft lists only seven:

1. Cross infection in the home;
2. Recall bias (for exposure);
3. Possible in-utero effects;
4. Social class;
5. Heating/cooking (one study);
6. Other illnesses (two studies);
7. Active smoking.

Conspicuously absent from the discussion in the Review Draft are the many published studies on other confounding factors which report no significant observations between parental smoking and childhood respiratory disorders.

For example, a number of reports have shown that the use of gas stoves in the home may be independently associated with childhood respiratory disease (Lebowitz, 1984; Harrington, 1985; Melia, 1977; Melia, 1979; Speizer, 1980). Other confounding factors independent of parental smoking have been reported recently in the medical literature. For example, studies have identified damp housing (Martin, 1987; Strachan, 1986; Platt, 1989) and father's occupation (Watkins, 1986) as potential explanatory factors for the occurrence of respiratory illness in children. Other recent studies have identified outdoor air pollution (Kerigan, 1986; Pope, 1989) infections transmitted during day-care attendance (Anderson, 1988) and the use of kerosene heaters and woodburning stoves in the home (Berwick, 1984; Osborne, 1989) as risk factors for childhood respiratory disease.

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The relevance of dampness in the etiology of respiratory symptoms in children is supported by current research which links dampness with the presence of molds, dust mites, fungi and other allergenic microbes. The growth of fungi and molds in the home is directly related to respiratory symptoms and sensitization to common allergens in children (Ownby, 1988).

Nutrition, the possible influence of respiratory cross-infection, family health practices and lifestyle are other possible confounders which received no mention in the analysis presented in Chapter 5.

The possible role of numerous confounders indicates that there is no "single alternative explanatory factor," as the Executive Summary suggests in its dismissal of the importance of confounding factors (1-9). Instead, the existence of so many confounding factors illustrates the difficulty in understanding the sources of childhood respiratory disease and the virtual impossibility of making a scientific or logical inference from ETS exposure alone to childhood respiratory disorders. Some examples from the scientific literature follow:

1. Anderson, L., et al., "Day Care Center Attendance and Hospitalization for Lower Respiratory Tract Illness," Pediatrics 82(3): 300-308, 1988.

   The suggestion made by our study and other studies was that for children <2 years of age, care outside of the home is an important risk factor for acquiring lower respiratory tract illness, as well as other infectious diseases, and that this risk can be reduced by using a day-care home instead of a day-care center.

   Smoking was less important than other risk factors in our study.

2. Berwick, M., et al., "Lower Respiratory Symptoms in Children Exposed to Nitrogen Dioxide From Unvented Combustion Sources," Environment International 15: 369-373, 1989.

   When socioeconomic status and history of respiratory illness were controlled, children under the age of seven exposed to 30 Hg/m^3 or more of nitrogen dioxide were found to have a risk of reporting lower

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respiratory symptoms 2.25 times (95% C.I. 1.69-4.79) that of children who were not exposed.
Exposure to environmental tobacco smoke was not significantly associated with reported symptoms in either age group.

3. Berglund, B., et al., "Radon, Passive Smoking, Particulates and Housing Epidemiology," Indoor Air 2: 255-260, 1984.

Using a staged design of air quality monitoring, we followed 174 families using unvented kerosene heaters and 173 families without heaters for a three-month period to evaluate the association between nitrogen dioxide (NO_2) exposure and acute respiratory illness rates.

Initial analyses indicate that exposed children have significantly more days of acute respiratory illness than controls.

There was no statistically significant difference in the mean number of cigarettes smoked daily in children's homes (12.63 exposed, 12.74 unexposed).

4. Brunekreef, B., et al., "Home Dampness and Respiratory Morbidity in Children," Am. Rev. Respir. Dis. 140: 1363-1367, 1989.

This study examined the relationship between measures of home dampness and respiratory illness and symptoms in a cohort of 4,625 eight-to 12-yr-old children living in six U.S. cities.

Odds ratios for molds varied from 1.27 to 2.12, and for dampness from 1.23 to 2.16 after adjustment for maternal smoking, gender, city of residence, and parental education.

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We conclude that dampness in the home is common in many areas of the United States and that home dampness is a strong predictor of symptoms of respiratory and other illness symptoms among 8- to 12-yr-old children.

5. Harrington, W. and Krupnick, Alan J., "Short-Term Nitrogen Dioxide Exposure and Acute Respiratory Disease in Children," JAPCA 35: 1061-1087, 1985.

> . . . higher ambient sulfate levels were found to have a positive effect on acute respiratory disease incidence in children over the entire period and for different subsamples, although this effect was not significant for either season analyzed separately.
>
> . . . we found no adverse effect of mother's smoking on children's health.

6. Holma, B. and Winding, O., "Housing, Hygiene, and Health: A Study in Old Residential Areas in Copenhagen," Archives of Environmental Health 32(2): 86-93, 1977.

> The effect of 109 social, medical, housing, and hygiene factors on morbidity of 2,096 individuals was studied in 881 apartments in Copenhagen. "Thriving" (satisfaction), followed by "housing standard" and "personal hygiene," turned out to be in the most prominent predictor for health.
>
> The negligible effects of tobacco and alcohol must be evaluated in the light of the fact that morbidity in this study covers morbidity in general. Furthermore, the influence of parents' tobacco smoking on the morbidity of the youngest children of 1-4 years of age, found by D.J. Hammer et al., could not be confirmed in our study.

7. Kerigan, A., et al., "A Three-Year Cohort Study of the role of Environmental Factors in the Respiratory

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Health of children in Hamilton, Ontario," Am. Rev. Respir. Dis., 133: 987-993, 1986.

> The relative importance of the effect of outdoor environmental factors (suspended particulates, sulphur dioxide) and indoor environmental factors (parental smoking, gas cooking), on the respiratory health of children is still unclear.
>
> There were 3,345 children 7 to 10 yr of age studied in the first year, a response rate of 95.4%, 3,727 in the second year, and 3,168 in the third year; 75.6% of the initial cohort were studied in both Year 2 and Year 3.
>
> The distribution of other covariables was not uniform, and the prevalence of parental smoking and gas cooking was greatest in the industrial area with the highest particulate pollution. Future analysis of these data will require the effect of these covariables to be distinguished from that caused by outdoor air pollution.

8. Martin, C., et al., "Housing Conditions and Ill Health," British Medical Journal, 294: 1987.

> . . . children living in damp houses, especially where fungal mould was present, had higher rates of respiratory symptoms, which were unrelated to smoking in the household, and higher rates of symptoms of infection and stress.

9. Melia, R.J.W., et al., "Association Between Gas Cooking and Respiratory Disease in Children," British Medical Journal, 149-152, 1977.

> A total of 5758 children aged 6 to 11 years from 28 randomly selected areas of England and Scotland were examined. In an analysis of the effects of health of possible indoor pollutants, boys and girls from homes

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in which gas was used for cooking were found to have more cough, "colds going to the chest," and bronchitis than children from homes where electricity was used. The girls also had more wheeze if their families used gas for cooking. This "cooking effect" appeared to be independent of the effects of age, social class, latitude, population density, family size, overcrowding, outdoor levels of smoke and sulphur dioxide and types of fuel used for heating. It was concluded that elevated levels of oxides of nitrogen arising from the combustion of gas might be the cause of the increased respiratory illness.

10. Melia, R.J.W., et al., "The Relation Between Respiratory Illness in Primary Schoolchildren and the Use of Gas for Cooking, I - Results From a National Survey," International Journal of Epidemiology, 8(4): 333-338, 1979.

The relation between the prevalence of respiratory illness and use of gas for cooking in the home has been investigated in a 5 year longitudinal study of primary schoolchildren from England and Scotland. 4827 boys and girls aged 5 to 10 years from 27 randomly selected areas were examined in 1977, the last year of the study. The prevalence of one or more respiratory symptoms or diseases was higher in children from homes where gas was used for cooking than in those from homes where electricity was used. The association appeared to be independent of age, sex, social class, number of cigarette smokers in the home and latitude but it was only found in urban areas....

11. National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, May 1-3, 1983, "Report of Workshop on Respiratory Effects of Involuntary Smoke Exposure: Epidemiologic Studies"

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The difficulty of controlling for potentially confounding variables was recognized. Such variables include: 1) unvented combustion products from different kinds of stoves used for both heating and cooking, e.g., gas, wood and kerosene, 2) other indoor pollutants such as formaldehyde and respirable particulate matter, 3) indoor pollutants of organic origin such as pollens, molds, mites, other allergens and infectious organisms, 4) characteristics of indoor environments such as temperature, humidity, and frequency of air exchanges, 5) socio-economic status, culture (ethnic), and such factors as crowding, number of siblings, household conditions, child care, reporting biases, etc., etc., 6) demographic and medical characteristics of the study population such as age, sex, marital status, the presence of underlying respiratory conditions, atopy, infections, disability and/or co-morbidity, 7) parental symptoms such as productive cough which will affect reporting, 8) maternal smoking during pregnancy, 9) annoyance responses and other psychological or social responses to tobacco smoking in a nonsmoker. Extensive as this list of potentially compounding variables may be, the importance of taking them into consideration in the study design and analysis cannot be overemphasized.

There are many potential confounding variables which must be taken into account. Data on these variables are not presently being collected uniformly among the studies underway.

12. Mitchell, E., et al., "Socioeconomic Status in Childhood Asthma," International Journal of Epidemiology, 18(4): 888-890, 1989.

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This study examines the relationship between socioeconomic status (SES) and asthma prevalence and the use of asthma medication. One thousand and fifty European children aged eight and nine years were studied by parents completed questionnaire and histamine inhalation challenge. After controlling for sex of the child and for smokers in the house there were significantly higher lifetime (P=0.029) and current (=0.046) prevalence rates of wheeze in children in low SES groups.

13. Nordvall, S.L., et al., "Sensitization of Children in the Stockholm Area to House Dust Mites," Acta Paediatr Scan, 77(5): 716-720, 1988.

Atopic sensitization of children in the Stockholm area to house dust mites (HDM) was investigated in a case-control study. Sixty children with and 60 without positive skin prick tests for HDM were matched for age and sex. HDM-sensitized children had previously more often lived in other areas known to be mite infested than the control children. Sensitization to mites was related to dampness in the homes, but no significant relationship was found to the type of residence, frequent visits to a summer house in the archipelago or parental smoking.

14. Osborne, J.S., "Health Effects of Heating With Wood: Chest Illness in Young Children and Indoor Heating with Woodburning Stoves," The Human Equation: Health and Comfort, Indoor Air Quality '89, April 17-20, 1989, San Diego, CA.

This study investigated a suspected relationship between the occurrence of chest illness in young children and use of woodburning stoves (WBS) for indoor heating.

. . . the WBS-group had a greater proportion of chest illnesses lasting

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at least one week (32% vs. 16%) and a greater proportion of hospitalizations for chest illness before age two years (16% vs. 10%). These differences were not accounted for by medical histories, frequency of physician visits, sociodemographic factors, or exposure to other sources of indoor air pollution investigated in the study (e.g., parental smoking, cooking with gas, urea-formaldehyde foam insulation) and suggest that indoor heating with WBS may be a significant risk factor for chest illness in young children.

15. Platt, S., et al., "Damp Housing, Mould Growth, and Symptomatic Health State," BMJ, 298: 1673-1678, 1989.

Objective -- To examine the relation between damp and mould growth and symptomatic ill health.

Measurements and main results - Damp was found in 184 (30-80%) dwellings and actual mould growth in 274 (45-9%). Adult respondents living in damp and mouldy dwellings were likely to report more symptoms overall, including nausea and vomiting, blocked nose, breathlessness, backache, fainting, and bad nerves, than respondents in dry dwellings. Children living in damp and mouldy dwellings had a greater prevalence of respiratory symptoms (wheeze, sore throat, runny nose) and headaches and fever compared with those living in dry dwellings. The mean number of symptoms was higher in damp and mouldy houses and positively associated with increasing severity of dampness and mould (dose response relation). All these differences persisted after controlling for possible confounding factors such as household income, cigarette smoking, unemployment, and overcrowding.

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16. Pope, C., "Respiratory Disease Associated with Community Air Pollution and a Steel Mill, Utah Valley," AJPH, 79(5): 623-628, 1989.

> Finally, the association between respiratory illness and particulate pollution found in this study is relatively large as compared with some previous studies. This relatively strong association can be explained in part because PM is a better indicator of particulate pollution as it relates to respiratory health than previously used indicators. Also, because Utah Valley experiences relatively high levels of particulate pollution, yet has an extremely low portion of its population that smoke, particulate pollution is likely a relatively large contributor to respiratory disease in the country.

17. Strachan, D. and Elton, R., "Relationship Between Respiratory Morbidity in Children and the Home Environment," Family Practice, 3(3): 137-142, 1986.

> The relationships between 12 features of the home environment and respiratory morbidity as reported by parents, and as recorded in general practice records, were studied in 165 children aged seven to eight years. Parental reports of wheeze, nocturnal cough and school absence owing to chest trouble were significantly more common among children with a family history of wheeze, and those from damp or mouldy housing. There were associations between coal fires and nocturnal cough and between an open window and wheeze. Multivariate analyses confirmed these associations to be independent of each other, and of the child's sex and seven other features of the home environment, including gas appliances and parental smoking. These same environmental variables were not consistently

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related to general practice consultations for wheeze or lower respiratory illness.

V. Other Reviews of the Literature:

It is noteworthy that Chapter 5 of the Review Draft is not consistent with recent objective reviews of the literature on parental smoking. Some of the conclusions of those reviews are:

1. Rubin, D. and Damus, K., "The Relationship Between Passive Smoking and Child Health Methodologic Criteria Applied to Prior Studies," The Yale Journal of Biology and Medicine, 61: 401-411, 1988.

> Most studies investigating the relationship between passive smoking and child health have found a significant effect on respiratory illness and lung function. The wide range of findings is based on diverse types of studies which use multiple criteria for respiratory illness, smoke exposures, and outcome variables. The aim of this review is to examine these studies in an attempt to focus attention on methodological criteria which relate to the strength of the association and likelihood of a causal relationship between passive smoking and child health.
>
> We examined 30 studies and judged their strength by examining (1) data collection, (2) surveillance bias, (3) definition of amount of smoking, (4) definition of illness, (5) detection bias, (6) outcome variables, and (7) control of confounding variables.
>
> While a few well-designed studies demonstrate a significant effect of passive smoking on child health, most studies had significant design problems that prevent reliance on their conclusions. Thus, many questions remain, and future studies should consider important

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methodological standards to determine more accurately the effect of passive smoking on child health.

2. Witorsch, R. and Witorsch, P., "Maternal Smoking and Pulmonary Performance in Children: A Critical Analysis," Indoor Air '87, Proceedings of the 4th International Conference on Indoor Air Quality and Climate, Vol. 2, 175-179, 1987.

Abstract. Thirteen of 18 epidemiologic reports reviewed herein have claimed that parental (usually maternal) smoking decreased pulmonary function in children. These reports exhibit significant discrepancies in the absolute and dose-related effects of parental smoking on the most prevalently used spirometric parameters (FEV and FEF_{25-75}) in children. These inconsistencies may reflect errors in estimating ETS exposure from questionnaire data, and/or inadequate attention to socioeconomic factors and other confounding variables. Furthermore, alternate explanations for apparent ETS effects, such as genetic aggregation of pulmonary function and maternal smoking during pregnancy and lactation have not been excluded. Additional studies, appropriately controlled, are necessary to answer the question of whether ETS impairs pulmonary function in children.

3. Witorsch, R. and Witorsch, P., "A Critical Analysis of the Relationship Between Parental Smoking and Pulmonary Performance in Children," Off. Gesundh.-Wes., 51(2): 78-83, 1989.

To date, at least 24 epidemiologic research papers, of essentially similar design, have been published on the effects of current or lifetime parental smoking on pulmonary function parameters in children.

A number of factors should be considered when interpreting the

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results of these studies, particularly in light of the observed inconsistencies and the fact that children were classified solely on the basis of questionnaire data. Among these are sources of misclassification bias, which could either underestimate or overestimate parental smoking effect, socioeconomic status, other variables, and genetic factors. Also, effects of maternal smoking in utero or on lactation, as well as exposure of the child to environmental tobacco smoke (ETS), need to be considered as possible causes of any apparent decrement in pulmonary function in children.

4. Witorsch, R., "Parental Smoking and Respiratory Health and Pulmonary Function in Children: A Review of the Literature and Suggestions for Future Research," Environmental Tobacco Smoke, Proceedings of the International Symposium at McGill University, 1989, pp. 205-226.

Inhalation of ETS by the young child could contribute to increased incidence of respiratory symptoms and illness. To date, however, ETS exposure has been presumed only on the basis of questionnaire data (usually parental smoking status).

Several factors other than ETS, however, alone or in combination with one another, may account for the association between parental smoking and impaired respiratory health in younger children. Among these are socioeconomic status and related factors, and biologic mechanisms other than ETS associated with the prenatal and early postnatal period.

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